PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 27894/700152	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/050058	International filing date *(day/month/year)* 30.01.2004	Priority date *(day/month/year)* 21.02.2003
International Patent Classification (IPC) or national classification and IPC A61K9/48, A61K31/404, A61P35/00		
Applicant PHARMACIA ITALIA S.P.A.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.09.2004	12.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schifferer, H Telephone No. +49 89 2399-7472

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050058

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-27 as originally filed

   Claims, Numbers

   1-19 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 8, 11
	No:	Claims	1, 3-7, 9, 10, 12-19
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	2, 8, 11
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Documents
The following documents (D1-D5) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 : WO 98/38984 A (SUGEN INC ; SHENOY NARMADA (US); WAGNER GREGORY S (US)) 11 September 1998 (1998-09-11)
D2 : WO 01/30351 A (JAMES CHRISTOPHER ; CIVAROLI PAOLA (IT); MUGGETTI LORENA (IT); MARTINI) 3 May 2001 (2001-05-03)
D3 : US 6 514 524 B1 (SASLAWSKI OLIVIER ET AL) 4 February 2003 (2003-02-04)
D4 : US 5 993 858 A (CRISON JOHN R ET AL) 30 November 1999 (1999-11-30)
D5 : US 2002/119198 A1 (MOROZOWICH WALTER ET AL) 29 August 2002 (2002-08-29)

Unless otherwise specified, reference is made to the respective cited passages in D1-D5 (see the International Search Report, Form PCT/ISA/210).

2) Novelty - Article 33 (1) and (2) PCT

2.1) D1-D5 disclose pharmaceutical compositions comprising components which are comparable to those concretized in present application:

- a hydrophobic active agent, in particular indolinone derivatives (see claims 3-5), cancerostatics (see present description)
- a surfactant agent constituted by polyglycolised glyceride, in particular Labrasol, Labrafil M2125; Labrafil M1944
- a carrier, in particular a saturated polyglycolised glyceride or a polymer with low melting point, e.g. Gelucire 44/14, Lutrol F68

In detail, D1-D5 describe the following compositions in detail:
D1:
active principle: indolinone derivative, anticancer, antimetastatic agents, kinase inhibitors, angiogenesis-controlling agents, hydrophobic agents
surfactant: Labrasol
carrier: Gelucire 44/14

D2:
active principle: camptothecin derivative
surfactant: polyglycolised glyceride, Gelucire
carrier: polyethylene glycol

D3:

active principle: hydrophobic agent
surfactant: polyglycolised glyceride, Labrasol, Labrafil, Gelucire
carrier: polyethylene glycol, Gelucire 44/14
The content of the active principle is 0.01-95 %, preferably 0.01-90%, more preferably between 0.1-90 %. For acamprosate, percentages of 47-51 % were used in said formulations. Thus the system proves high percentage loading of the active ingredient.

D4:
active principle: lipophilic agent
surfactant: Labrasol
carrier: Gelucire 44/14

D5:
active principle: lipophilic agent
surfactant: polyglycolized glycerides
carrier: polyethylene glycol as solvent

All aforementioned formulations include a semisolid matrix or structure, which is filled in capsules. D1 and D2 explicitly disclose the manufacture of a medicament for treating cancer.

In the manufacturing process described in D1, Gelucire 44/14 is melted or Labrasol heated, the hydrophobic pharmaceutical agent is given into this mixture. Other excipients are added. The liquid melt is filled into a capsule. The Gelucire-based formulations are semi-solid at room temperature.

2.2) In the light of D1 -D5 (see section V-2.1), the subject-matter of claims 1, 3-7, 9, 10, 12-19 is considered not novel according to Article 33 (1) and (2) PCT.

2.3) Consequently, - under consideration of V-2.1, 2.2. - the subject-matter of claims 2, 8, 11 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D5.

3) Inventive Step - Article 33 (1) and (3) PCT

3.1) The problem posed in the present application was the galenical improvement of bio-pharmaceutical properties of active agents with a poor solubility in a physiological fluid.

The solution according to the Applicant was a pharmaceutical composition comprising (a) an active ingredient poorly soluble in water and present in a quantity of 15-45 % by weight, (b) a surfactant agent constituted by a polyglycolized glyceride and (c) a pharmaceutically acceptable hydrophilic carrier.

D1 which is regarded closest prior art discloses oral formulations comprising an indolinone derivative, but also other anticancer or antimetastatic agents, kinase inhibitors, hydrophobic agents, angiogeneis-controlling agents and polyglycolized lipids, wherein the active principle is added to a mixture of Labrasol and Gelucire 44/14. Bioavailability studies comparing the drug release from various polyglycolized lipid matrix preparations proved immediate and increased release for this

type of formulation.

D1 does not disclose high loading of the formulation with the active principle (15-45 %, 20-40 %), formulations on the basis of Gelucire 44/14/Lutrol F68 and on the basis of Lutrol F68/Labrasol.

D3 describes capsule presentations comprising a lipophilic agent (such as acamprosate), a polyglycolised glceride (Labrasol) for promoting absorption and Gelucire 44/14. Acamprosate is contained in percentages of 47-51 %, thus proving the high loading of an active agent in such formulations.

It appears to be obvious to a person skilled in the art to derive the use of the active pricniple in higher quantities (namely up to 45 %) from combining D1 with D3 and the use of Lutrol F68 in combination with Gelucire 44/14 from common galenical experience and textbook knowledge.

Unexpected or surprising effects do not seem to be connected with the high quantities of the active principle and the combinations of Gelucire 44/14/Lutrol F68 as well as Lutrol F68/Labrasol in comparison to the state of the art.

3.2) Therefore, under provision of V-3.1, the subject-matter of claims 2, 8, 11 is obvious to a person

skilled in the art due to general textbook knowledge. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

4) Further remarks

The Applicant's attention is drawn to the fact that the application must not be altered thus that its subject-matter might exceed the contents of the application originally filed (Article 41 (2) PCT).